A Genome-Wide Screen Reveals a Role for microRNA-1 in Modulating Cardiac Cell Polarity.

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Public Summary:
Many molecular pathways involved in heart disease have their roots in evolutionarily ancient developmental programs that depend critically on gene dosage and timing. MicroRNAs (miRNAs) modulate gene dosage after the process of transcription, which is when a complementary strand of RNA is created from a sequence of DNA. One miRNA that appears only in muscle cells, called miR-1, is particularly important for developing and maintaining skeletal and heart muscle. To identify pathways regulated by miR-1, we used genetic screening techniques in fruit files and identified several unexpected genes that genetically interacted with dmiR-1. One of these genes, called kayak, encodes a developmentally regulated transcription factor, which is a protein that binds to specific DNA sequences to control the flow of genetic information from DNA to mRNA. Additional studies directed at this genetic relationship revealed a previously unappreciated function of dmiR-1 in regulating the orientation of intracellular structures of cardiac progenitor cells. The mammalian version of kayak, c-Fos, was dysregulated in hearts of gain- or loss-of-function miR-1 mutant mice in a stress-dependent manner. These findings illustrate the power of fruit fly genetic screens to find points of intersection between miRNAs and molecular pathways that have remained the same throughout mammalian evolution.

Scientific Abstract:
Many molecular pathways involved in heart disease have their roots in evolutionarily ancient developmental programs that depend critically on gene dosage and timing. MicroRNAs (miRNAs) modulate gene dosage posttranscriptionally, and among these, the muscle-specific miR-1 is particularly important for developing and maintaining somatic/skeletal and cardiac muscle. To identify pathways regulated by miR-1, we performed a forward genetic screen in Drosophila using wing-vein patterning as a biological assay. We identified several unexpected genes that genetically interacted with dmiR-1, one of which was kayak, encodes a developmentally regulated transcription factor. Additional studies directed at this genetic relationship revealed a previously unappreciated function of dmiR-1 in regulating the polarity of cardiac progenitor cells. The mammalian ortholog of kayak, c-Fos, was dysregulated in hearts of gain- or loss-of-function miR-1 mutant mice in a stress-dependent manner. These findings illustrate the power of Drosophila-based screens to find points of intersection between miRNAs and conserved pathways in mammals.